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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,539	07/16/2003	H. William Bosch	029318-0961	6324

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

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10/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/619,539	BOSCH ET AL.	
	Examiner	Art Unit	
	S. Tran	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-35,37,39,41,43-52,54-82 and 84-123* is/are pending in the application.

4a) Of the above claim(s) *46-52,54-82 and 84-123* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-35,37,39,41 and 43-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/07/08;09/10/08;09/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

Claims 1-4, 6, 8-24, 26-30, 32-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge US 6,267,989, in view of Straub et al. US 2002/0142050 A1.

Liversidge teaches a method for preventing crystal growth and aggregation in nanoparticulate composition (abstract). The nanoparticulate composition comprising nanoparticulate drug and two or more surface stabilizers adsorbed to the surface of the drug (column 6, lines 45-59). Drugs comprise poorly soluble drugs (column 7, lines 4-31). Drugs are in crystalline or amorphous states (column 3, lines 41-50). Drug is used in an amount from about 99.9% to about 10% (column 9, lines 9-14). Surface active agents are disclosed in column 7, lines 39 through column 8, lines 1-36. Surface active agents are used in an amount of from about 0.1% to about 90% (column 9, lines 4-8). Liversidge further teaches the effective average particles size of the nanoparticle is at least about 95% of the particles have an average particle size of from about 150 nm to about 350 nm (column 8, lines 37-54). The nanoparticulate composition is suitable for parenteral administration in the form of dispersion, suspension or emulsion in aqueous or non-aqueous solutions (column 10, lines 4-34 and 55-67). The nanoparticulate composition also contains adjuvants such as preserving, wetting, emulsifying, and dispensing agents (column 10, lines 25-30).

Liversidge does not expressly teach the crystal growth inhibitor.

Straub teaches the use of sugar such as mannitol to inhibit crystal growth for drugs in an amorphous or crystalline state (paragraphs 0082-0083). Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Liversidge to include sugar to obtain the claimed invention. This is because Straub teaches the use of sugar as a bulking agent, wetting agent, or anti-crystallization agent to prevent crystal growth for drugs in crystalline state, because Straub teaches the use of mannitol to inhibit crystal growth for drugs in crystalline state is well known in the art, and because Liversidge teaches the desirability to prevent crystal growth for poorly soluble crystalline state drugs (column 3, lines 35-43), and because Liversidge teaches the use of other excipients in the nanoparticulate composition such as wetting agent. Therefore, one of ordinary skill in the art would have been motivated to combine surface modifiers, mannitol as an anti-crystallization, and nanoparticle drug with the expectation of additive affect in preventing crystal growth in nanoparticulate composition to obtain a nanoparticulate composition that exhibit prolonged particle size stability even following exposure to elevated temperatures.

Claims 25, 30-35, 37, 39, 41 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge US 6,267,989, in view of Straub et al. US 2002/0142050 A1 and Liversidge US 2005/0004049 (Liversidge '049).

Liversidge is relied upon for the reason stated above. The reference does not teach the claimed specific active agent suitable in a bioadhesive composition.

Liversidge '049 teaches a nanoparticulate composition comprising surface modifier, and a drug having solubility of less than about 30 mg/ml (abstract; and

paragraph 0045). Drug including analgesic, NSAID and vitamins are discloses in paragraphs 0109-0113). The nanoparticulate composition is processed into a liquid dosage for bioadhesive composition (paragraphs 0081-0089). Liversidge further teaches the claimed viscosity, C_{max}, T_{max}, and bioequivalency (paragraphs 0090-0105). Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Liversidge to include active agents in view of the teaching of Liversidge '049 to obtain a useful bioadhesive composition of the present invention. This is because Liversidge '049 teaches the desirability to incorporate the claimed active agents in the nanoparticulate composition, and because Liversidge teaches a stable nanoparticulate composition suitable for a wide variety of active agents.

Claims 1-6, 8-10, 12, 14-15, 17, 21-24, 26-30 and 32-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bagchi et al. US 5,665,331, in view of De Garavilla et al. US 5,834,025 and Straub et al.

Bagchi teaches a nanoparticle having average particle size less than 300 nm, the nanoparticle comprising pharmaceutical active agent, one or more surface stabilizers, and a crystal growth modifier (abstract; column 3, lines 16-62; and column 6, lines 49-55). Active agents include poorly soluble agent such as nsaid (column 5, lines 14-55). Active agents are in crystalline phase (column 5, lines 8-12). Surfactants are disclosed in column 6, lines 1-49). Additional surfactant is disclosed in column 6, lines 56-62). Surfactant is used in an amount ranging from 0.1-90% by weight based on the total

weight of the dry particle (column 7, lines 1-5). Crystal growth modifier is used in an amount of between 1-40% by weight (column 11, lines 65-67). The obtained nanoparticles are suitable for the parenteral or oral administration in liquid dosage form (column 7, lines 6-51).

Bagchi does not expressly teach the pharmacokinetic profiles such as the AUC, Cmax, and Tmax. However, such limitations are inherent because Bagchi teaches the same nanoparticle comprising the same materials require by the present invention, namely, nanoparticle having average particle size less than 300 nm comprising a drug, a surface modifier, and a crystal growth inhibitor.

Bagchi does not explicitly teach the use of glycerol and mannitol in the composition.

Straub teaches the use of sugar such as mannitol to inhibit crystal growth for drugs in an amorphous or crystalline state (paragraphs 0082-0083).

De Garavilla teaches a nanoparticulate composition comprising the use of tow or more surface modifiers including glycerol (abstract; and column 9, lines 59-67).

Thus, it would have been obvious to one of ordinary skill in the art to modify the nanoparticulate composition of Bagchi to include sugar such as mannitol, and surface modifier including glycerol, in view of the teachings of De Garavilla and Straub. This is because Straub teaches the use of sugar as anti-crystallization agent to prevent crystal growth for drugs in crystalline state, because De Garavilla teaches the use of glycerol as a surface modifier to prevent aggregation of drugs in nanoparticles size, because Bagchi teaches the use of crystal growth inhibitor, and because Bagchi teaches the use

of surface modifier to minimizing the close, interparticle approach necessary for agglomeration and flocculation, thus obtaining a stable nanoparticulate composition.

Response to Arguments

Applicant's arguments filed 07/03/08 have been considered but are moot in view of the new grounds of rejection.

Applicant argues that Bagchi does not teach the claimed crystal growth inhibitor, and therefore, fails to teach each and every aspect to anticipate the claimed invention.

In response to applicant's argument, the 102(b) rejection by Bagchi et al. has been withdrawn in view of applicant's amendment.

Applicant argues that by Bagchi's definition, a crystal growth modifier must posses at least 75% identity in chemical structure to the active agent. Exemplary crystal growth modifiers are listed at column 11. The Examiner suggested use of glycerol and mannitol in the claimed composition based on the teachings of De Garavilla and Straub. One skilled in the art would have had no reason to substitute Bagchi's crystal growth modifier for either glycerol or mannitol. Tiffs is because glycerol and mannitol do not posses the requisite 75% chemical identity to the active agent. Thus, the Examiner's suggested combination would be inapposite to the express teaching of suitable crystal growth modifiers in Bagchi and would not be suitable for the intended purpose of Bagchi.

However, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is noted that the crystal growth modifiers listed at column 11 are just exemplary, and are solely for the X-ray contrast agents (column 11, lines 56-65). Further, independent claim 1 of the present invention does not even identify the active agent. Thus, active agent can be any compound similar to that of the claimed crystal growth inhibitor. This is evident by the present claims 29 and 30, recite active agent includes minerals, healing foods, whole foods, food additives, and oils such primrose, fish, and marine animal oils. Mannitol, sucrose, glucose, fructose, lactose, mannose, xylitol, sorbitol, trehalose, sugar, and polysaccharide are well known food additives. Accordingly, the 103(a) rejection over Bagchi in view of De Garavilla and Straub is maintained.

Applicant argues that Liversidge solves the issue of crystal growth and aggregation in nanoparticulate compositions without using any crystal growth inhibitor, as such, one skilled in the art would have had no reason to incorporate a crystal growth inhibitor taught by Straub into the compositions of Liversidge to prevent crystal growth.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Liversidge teaches the use of other excipients in the nanoparticulate composition such as wetting agent. Further, Liversidge teaches the desirability to prevent crystal growth for poorly soluble crystalline state drugs (column 3, lines 35-43). Straub teaches the use of sugar as a bulking agent, wetting agent, or anti-crystallization agent to prevent crystal growth for drugs in crystalline state. Straub further teaches the use of mannitol to inhibit crystal growth for drugs in crystalline state is well known in the art. Therefore, one of ordinary skill in the art would have been motivated to combine surface modifiers, mannitol as an anti-crystallization, and nanoparticle drug with the expectation of additive affect in preventing crystal growth in nanoparticulate composition to obtain a nanoparticulate composition that exhibit prolonged particle size stability even following exposure to elevated temperatures.

Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to S. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 8:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. Tran/
Primary Examiner, Art Unit 1618